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REPRINTED FROM THE AMERICAN JOURNAL OF PHYSIOLOGY
Vol. 95, No. 2, November, 1930

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Reprinted from THE AMERICAN JOURNAL OF PHYSIOLOGY
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CIRCULATORY CHANGES DURING PERIODIC VENTILATION WITH APNEAS PRODUCED BY MARKED CURTAILMENT OF BLOOD FLOW TO THE BRAIN[1,2]

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Received for publication August 20, 1930

In the previous paper a form of periodic respiration was described, characterized by periodic changes in ventilation with apneas virtually lacking. The present paper deals with periodic ventilation with prolonged apneas, produced by a greater impairment of circulation than employed in the previous paper.

METHODS. The experiments were carried out on dogs which were anesthetized with morphine and urethane or with amytal. Periodic ventilation was brought about by one of the three methods: 1, ligation of spinal arteries in conjunction with method 3, virtually giving complete control of the blood flow to the head. This method was used in obtaining figures 2A and 2B. It was adopted because the spinal artery is often alone sufficient to supply an adequate amount of blood to maintain even respiratory function; 2, increased intracranial pressure, by the use of a brass tube inserted into a trephined opening in the parietal bone with the dura mater incised to permit passage of fluid under pressure into the subdural spaces. This procedure is essentially the same as that reported by Eyster (1906). This method was used in obtaining figure 3; 3, occlusion pressure applied to a cerebral artery by the use of a pressure cuff surrounding the vessel (this was considered in detail in the previous paper) along with occlusion of other arteries. This method was used in obtaining figures 4A and 4B.

The operative procedure in the first method is briefly as follows. The vagus nerves and the common carotid arteries were isolated and kept intact. In the region of the second cervical vertebra, the vertebral arteries were ligated and divided at their exit from the vertebral canal and all remaining tissue exterior to the second cervical vertebra excepting the common carotids and vagus nerves was divided by cautery. The posterior bony arches of the second cervical vertebra were then cut by means of

[1] Preliminary report appeared in the Proceedings of the Society for Experimental Biology and Medicine, 1929, xxvi.

[2] A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

an electric rotary saw, the spinous process removed, and the dura mater incised. By placing a silk ligature around the dentate ligaments, the cord was elevated sufficiently to secure a ligature around the spinal artery. The smaller spinal arteries lying in the lateral sulci were then ligated. The venous return from the head was maintained by the spinal sinuses. To prove the effectiveness of this method in controlling the blood flow to the brain, the operation just described was performed and all cerebral arteries in the region of the second cervical vertebra were occluded and heparin added to prevent coagulation of the blood. Within a few minutes after the death of the animal, an aqueous solution of eosin was injected under 120 mm. mercury pressure into the trunk of the animal by way of the femoral arteries. The entire trunk of the animal became stained as well as the cord posterior to the level of the tie of the spinal arteries. The cord anterior to the tie remained unstained. This staining is shown by the black shading in figure 1 in the longitudinal and cross sectional views of the cord at different levels.

The methods described in the previous paper for recording blood pressure, respiration, the electrometric recording of blood flows, etc., are the same as those used in the present paper.

Results. Figures 2A and 2B are continuous records of one experiment. The experimental procedure was method 1 which included the ligation of the spinal arteries. Records were obtained of femoral arterial mean blood pressure, respiration, occlusion pressure applied to one carotid artery, left common carotid blood volume flow, femoral arterial blood flow, and time in seconds. The continuous thermoelectric method was utilized for the blood volume flows. The anesthetic used was urethane and morphine.

Previous to figure 2A, the right carotid artery was occluded leaving the left carotid artery as the sole source of blood to the head. Figure 2A shows the application of occlusion pressure on the left carotid at *1*, *2*, *3*, and *4*. The occlusion pressure at *1* was raised to a point considerably below mean blood pressure. This occlusion pressure is maintained until point *2*. During the period *1* to *2*, there is no significant change in the carotid or femoral blood flows, heart rate, mean blood pressure or respiration. At *2* the occlusion pressure is raised slightly higher and maintained at this new level until point *3*. Respiratory minute volume is increased thirty per cent coincident with the significantly lowered carotid blood flow. Heart rate, mean blood pressure, and femoral blood flow are not altered appreciably. A further decrease in carotid blood flow is obtained by again raising the occlusion pressure at *3*. This new level of occlusion pressure was maintained through the period *3* to *4* and was accompanied by a decrease in carotid flow, no changes in mean blood pressure and a further increase of respiratory minute volume of fourteen per cent, or an increase over the preocclusion pressure period (to the left of *1*) of 44 per cent. Femoral blood

flow and heart rate are not significantly altered during this period. At *4* the occlusion pressure was raised to equal mean blood pressure. Following this procedure the mean blood pressure rose slightly, but fell below the occlusion pressure at *5*. During the early part of the period *4* to *5* respiratory stimulation increased still further, but the remainder of this period showed respiratory depression. At the onset of period *5* to *6* mean blood pressure fell below the occlusion pressure. This period was accompanied by marked decreased carotid flow and decreased heart rate. In the early part of this period, *5* to *6*, respiration terminated in apnea, lasting

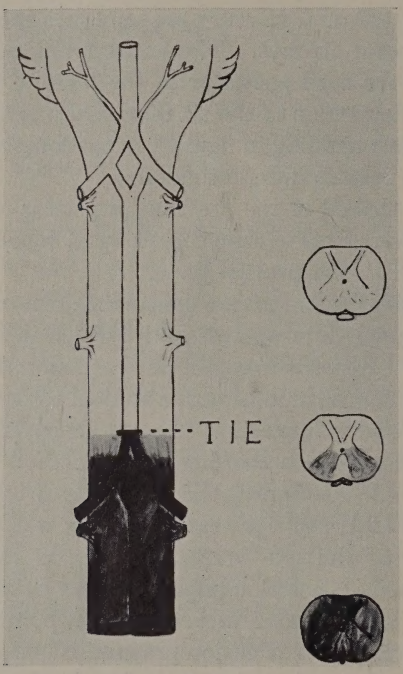
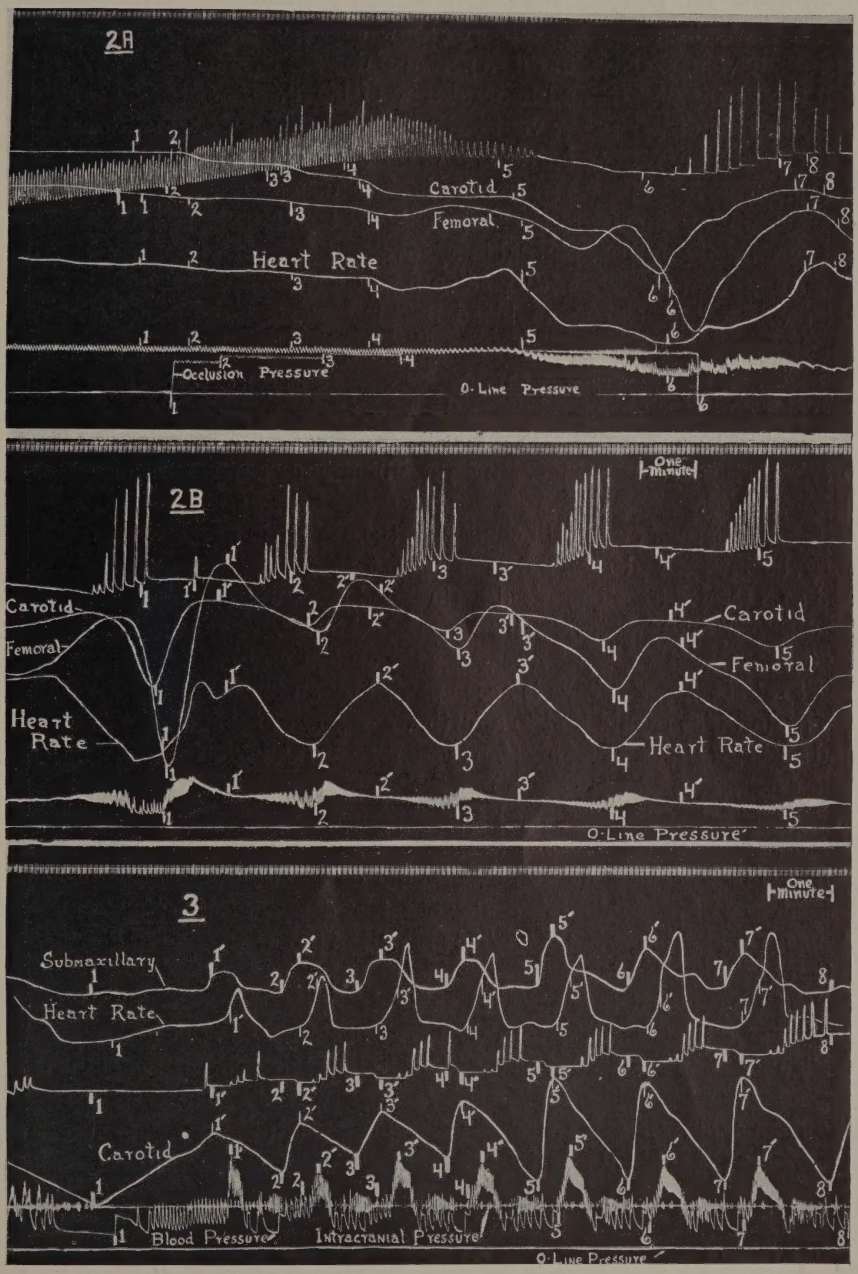


Fig. 1

two minutes and seventeen seconds. The occlusion pressure was removed at *6*, and twenty seconds later a group of respiratory movements was initiated. This group of thirteen respirations began just before the deocclusion of the right carotid at *7* and the injection of 100 cc. of glucose-saline at *8* with a small depth and increased to a maximum. Ventilation then decreased ending in apnea. Apnea, slow pulse rate, reduction in blood flow and mean blood pressure go hand in hand. With removal of occlusion pressure at *6*, increase of heart rate, blood flow and ventilation follow coincidently.


2A
Carotid
Femoral
Heart Rate
Occlusion Pressure
0-Line Pressure
2B
One Minute
Carotid
Femoral
Heart Rate
0-Line Pressure
3
Submaxillary
Heart Rate
Carotid
Blood Pressure
Intracranial Pressure
0-Line Pressure

Figs. 2A, 2B, 3

In figure 2B, periodic ventilation is well established. Corresponding points marked on all of the records show that pulmonary ventilation of increasing volume occurs during a period of decreasing mean blood pressure and decreasing carotid and femoral flow of blood. Toward the close of these periods of increasing ventilation, mean blood pressure and volume flow of blood increase and after 1, 2, or 3 breaths apnea is suddenly established. The final breaths show a distinct decrease in rate. Periodic changes in heart rate (minimum 60, maximum 204) are visible on the blood pressure tracing and are plotted in the overlying curve. Heart rate corresponds more accurately with volume flow changes in the carotid artery than with changes in mean blood pressure, possibly indicating a preponderance of central chemical control over arterial reflex control. It will be seen that increased heart rate comes on during increased cerebral flow of blood and after increased pulmonary ventilation. It might, therefore, be interpreted as a result of recovery of the cardio-inhibitory center from previous stimulation produced by a combination of apnea and decreased flow of blood.

The sequence of events which present themselves in figure 2B, may possibly be interpreted as follows. Respiratory stimulation occurs during and as a result of the decreased brain blood flows which are accompanied by decreasing heart rate from increased vagal tonus. The oxygen supplied by the increased ventilation removes the central vagal inhibition and the heart rate increases. This is accompanied by an increased blood flow to the brain which should lead to a further recovery of the inhibitory centers and a still greater increase in mean blood pressure and volume flow of blood. The excessive chemical changes in the respiratory center from increased flow of blood and accentuated ventilation results in apnea. The next blood to leave the lungs going to the brain is now deficient in oxygen and contains more carbon dioxide than it did during the respiratory period. Stimulation of the inhibitory center effects a decrease in heart rate and a decrease in blood flow to the brain as the blood pressure falls. The stimulation of respiration is finally brought about by the cumulative effects of lack of oxygen and the increased acidity resulting from apnea which is accentuated by the significant decrease of blood flow to the brain.

Figure 3 is an example of periodicity produced by increased intracranial pressure. Femoral blood pressure, respiration, the venous return from the submaxillary gland followed by the external drop method, the left common carotid blood flow followed by the thermoelectric method, intracranial pressure, and time in seconds were simultaneously recorded.

Previous to figure 3, intracranial pressure was raised to a point slightly below that of mean blood pressure. There was temporary stimulation of respiratory movements which gave way to gradual depression terminating in apnea of two minutes and forty-seven seconds' duration. The last three

respirations preceding this initial apnea are shown in the figure. Following the single respiratory movement at the end of this apnea, periodicity is thoroughly established. This initial respiratory movement occurs during the increased flow of blood and increased mean blood pressure, and in this respect resembles the group of increasing respiratory movements to the right of *6* in figure 2A, which also occurs during recovery with increasing blood flow. Following this initial respiratory movement there is a sudden increase in mean blood pressure which undoubtedly is accompanied by a greater increase in blood flow than that indicated on the volume flow record, for the thermopile vessel used in this experiment had considerable lag. Coincident with this suddenly increased blood pressure apnea occurs, and this may possibly be compared again with the development of apnea in figure 2A which followed augmented blood flow upon deocclusion of the carotid artery. Following the sudden increase in blood pressure, the first periodic fall in blood pressure occurred, and this is accompanied by the first respiratory group of periodicity. It, therefore, appears that the initial respiratory movement *1′* is interposed between a depression and a recovery apnea. (These terms will be amplified.) If true, it indicates how quickly depression, recovery, and stimulation give way to each other in the respiratory center.

In analyzing the established periodicity, the maximum and minimum carotid blood flows are used as points of reference. Laying these off on the records of ventilation and circulation we can consider the details of one cycle of this periodicity from *2′* to *3′*. Respiratory movements increase in amplitude during the decrease in blood flow. This augmentation then suddenly gives way to apnea, also during the decreasing blood flow. This apnea is then continued throughout the period of increased flow of blood from *3* to *3′* and even into the early part of the next period of decreased flow. These findings hold essentially in each periodic group.

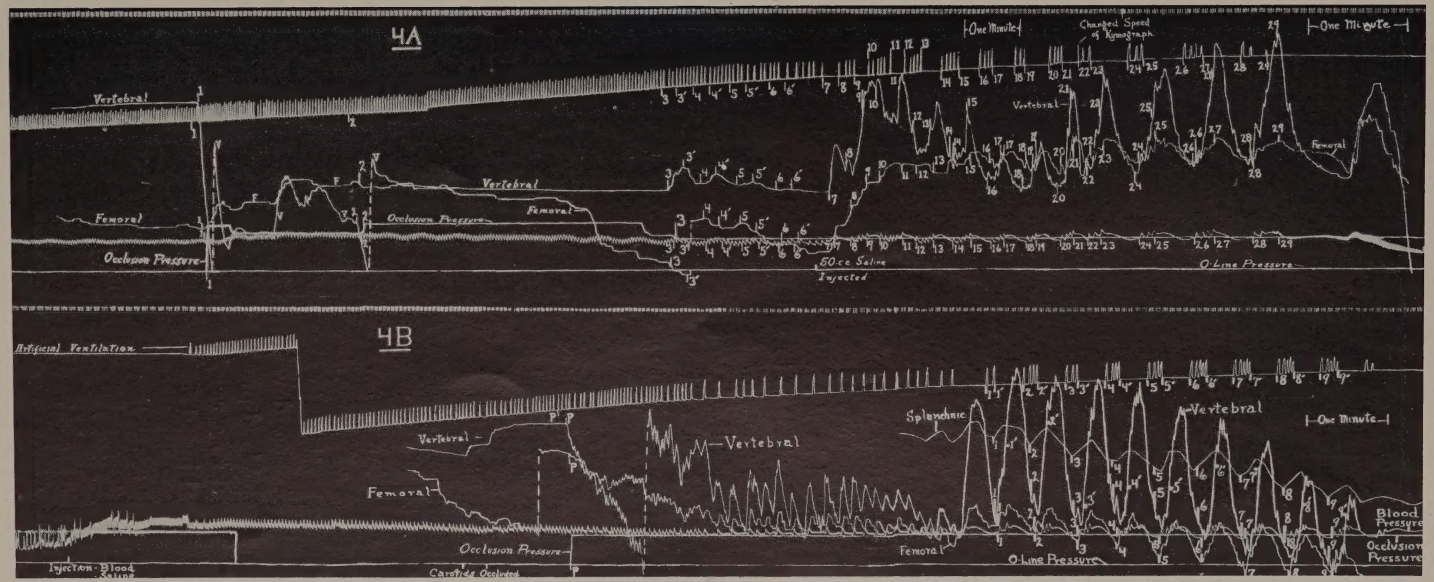
The carotid blood flow and the submaxillary venous flow follow, in general, the changes in mean blood pressure. This is not true of the heart rate. During the increase in blood pressure, heart rate and blood pressure run parallel, but heart rate continued to rise after mean blood pressure has started to fall, and diminishes again before mean blood pressure has reached its lowest level. At *3′*, blood pressure has reached its maximum, but heart rate continues to increase. The relation of heart rate to mean blood pressure is similar to that noted in figure 2B.

In figure 3, the onset of the respiratory movements of each respiratory group occurs during the period of decreased blood pressure and carotid blood flow agreeing with the results in figure 2B. The time relation of the development of apnea, however, was somewhat different. In figure 3 apnea begins towards the end of decreased carotid flow, whereas in figure 2B, apnea begins during the early part of the subsequent increased flow.

It is accordingly pointed out that the apneas of 2B were associated with a recovery process. This type of apnea may, therefore, be termed a recovery apnea. In contrast, the apneas of figure 3 are associated with a depression process as they occur in general during the decreased flow of blood. These may be designated as depression apneas. Although the onset of the apneas appear in general during the decreased blood flows, slight variations occur at *4* and *8*. The respiratory movement at *4* occurs late, that is, after the completion of the main body of respiratory movements. This may have its explanation in the observation that the last respiratory movement of each respiratory group shows a tendency to lag (see fig. 2B also). For example, note the respiratory group *1′* to *2*. The interval just to the left of *4* may, therefore, possibly be regarded as a reduction in rate of respiratory movements. The respiratory group *7′* to *8* represents a different variation. By extending the rate of respiration of this group it will be seen that the increased flow of blood at *8* begins before the point at which another (hypothetical) respiratory movement would take place. Accordingly the apnea to the right of *8* could be looked upon as a recovery apnea. Thus the increased flow may have prevented this hypothetical respiration. On the other hand, the increased flow at *8* following so closely upon the respiratory group indicates that a depression apnea may have actually started at the moment of the increased flow of blood. Thus depression and recovery apnea may indistinguishably shade into each other. However, conditions may occasionally arise depending upon the prevailing circumstances which would interpose a single respiratory movement between a depression and recovery apnea. Such conditions possibly obtain in regard to the initiating respiratory movement at *1′*.

Returning to a comparison of figure 3 and 2B, if we add one hypothetical respiratory movement to cycle *7′* to *8*, there is closer resemblance between figures 2B and 3. With this addition, apnea would also develop during the increasing flow of blood and could, therefore, be looked upon as a recovery apnea similar to those occurring in figure 2B. It is thus suggested that the conditions in figures 2B and 3 may be more similar than the records indicate and that the suddenness of chemical changes brings about more apparent rather than real differences.

Figures 4A and 4B are continuous records of another experiment. The procedure used in obtaining figures 4A and 4B was the third method. The central end of the left vertebral artery was connected to the peripheral end of the right vertebral artery through a volume flow thermopile and a pressure cuff applied to permit graded occlusion. Previous to figure 4A the carotids were occluded, thus leaving one vertebral artery and the spinal arteries to supply blood to the brain. The continuous thermoelectric method of recording was used for the vertebral and femoral blood flows. Femoral blood pressure, respiration, occlusion pressure, blood flows, and


4A
Vertebral
Femoral
Occlusion Pressure
One Minute
Changed Speed of Kymograph
50 cc Saline Injected
0 Line Pressure
4B
Artificial Ventilation
Vertebral
Femoral
Occlusion Pressure
Splanchnic
Injection - Blood
Carotids Occluded
Blood Pressure
Occlusion Pressure

Figs. 4A, 4B

time in seconds were simultaneously recorded. Dotted lines indicate the raising of the writing points to keep them on the record. The anesthetic used was amytal.

Occlusion pressure on the vertebral artery was increased at *1* to a point considerably above mean blood pressure. There was temporary stimulation of respiratory movements which gave way to a very short apnea just preceding the increased vertebral flow at about the middle of the period *1* to *2*. This increase in vertebral flow is associated with an increase of mean blood pressure and is followed by a second increase accompanied by another increase in blood pressure. At *2* the occlusion pressure was raised considerably above mean blood pressure resulting in a complete obstruction of the vertebral artery. During the period *2* to *3* blood flow reached the brain by way of the spinal arteries only. Respiratory movements were maintained at a slower rate and greater amplitude than prior to *1* where vertebral blood flow was copious. At *3* the occlusion pressure was lowered and vertebral blood flow was reëstablished when blood pressure increased sufficiently to overcome the occlusion pressure. The waves in mean blood pressure are reflected in the vertebral flow record.[3] The periodicity in ventilation was rather indefinite which would correspond to the relatively small changes in volume flow of blood. At number *7* the center was depressed and responded well to the subsequent larger variations in blood flow. At the end of *4A* artificial ventilation and saline solution were administered to resuscitate the animal. A second series of responses similar to those shown in *4A* was then elicited by a subsequent reduction in volume flow of blood.

Partial occlusion of the vertebral artery at *P* brought about a marked decrease in the vertebral blood flow. There was temporary stimulation of respiratory movements which gave way to gradual slowing of the rate, accompanied by a slight increase in amplitude. With each respiratory movement there was a change in vertebral blood flow which was, presumably, secondary to the respiratory movements. Mean blood pressure gradually decreased until it was almost equal to the occlusion pressure. This brought about a further decrease in vertebral blood flow, when suddenly periodic fluctuations in mean blood pressure and vertebral flow of blood appeared. Apnea develops with the first increase in vertebral blood flow and mean blood pressure. These large circulatory changes can hardly be attributed to a respiratory movement. Since the initial large increase in vertebral blood flow had its onset during the last respiratory

[3] Attention is called to the increase of vertebral blood flow occurring slightly later than the increase of the femoral and splanchnic flows as this lack of synchronism might be misinterpreted. It is probably due to the fact that the occlusion pressure applied to the vertebral artery does not allow an increase of blood through the artery until the arterial blood pressure is sufficient to overcome the occlusion pressure.

movement preceding the initial apnea, this apnea could be regarded as secondary to improved circulation. It is, therefore, considered as a recovery apnea. This recovery apnea marks the establishment of periodicity.

The points of reference used in analyzing figure 4A and 4B are different than those used in the previous figures. The beginning and end of each respiratory group is set off on the vertebral blood flow and mean blood pressure records and only the beginning of the respiratory group is marked off on the femoral, splanchnic, and blood pressure records. (The splanchnic venous blood flow was followed by the external drop method.) The onset of respiratory movements during periodicity occurred, as in the previous figures, after a period of decreased blood pressure and decreased blood flow, and continued into the increased blood pressure and increased blood flows. In this respect the results are similar to figure 2B. Respiration was initiated on the average about 11 seconds after the onset of the decreased blood flows. In figure 3 respiration began about 25 seconds after the decreased blood flows was initiated and in figure 2B it began more than a minute later. The periodic changes in circulation occur abruptly and are of extremely short duration, but at the crests and troughs, blood flow changes occur more slowly. These high and low flows are, therefore, of relatively long duration. Assuming a good recovery during the high blood flows there is little time for altered chemical changes during the rapidly decreasing flow. Furthermore, the center may now be in a condition to withstand a short period of decreased flow without responding with marked stimulation. Agreeing with this we find that the first respiration occurs in the trough of the volume flow record during which the respiratory center presumably continues to be stimulated. Blood volume flow now suddenly increases, but again the period of increase is too short to compensate the previous lack of blood and thus occasionally the last respiration may occur well up on the ascending limb of the volume flow record. If we draw a line of mean blood volume flow across the record it may be stated as a gross approximation, that on the whole respiratory movements occur during lowered blood flows and pressures and that apneas occur during increased blood flows and pressures.

Heart rate did not show periodicity in figure 4B. This constancy of rate, indicating lack of change of vagal tone was common in all experiments in which amytal was used as the anesthetic. Even with increased intracranial pressure cardiac slowing was lacking when amytal was used. This is in contrast to the marked changes in heart rate in figure 3 in which urethane and morphine was the anesthetic. This constancy of heart rate, together with the marked changes in mean blood pressure suggest periodicity of the vasomotor center. It was hoped that direct evidence of active periodic vasoconstriction and dilatation would be obtained by recording the various blood flows throughout the series. As seen in figure 4B, the splanchnic and

femoral blood flows follow the changes in mean blood pressure. The results, however, do not necessarily prove that active vasomotor changes are absent. It is possible that the increased driving head of pressure is accompanied by either an active vasoconstriction or vasodilatation. Experiments using a constant perfusion pressure through tissue isolated from the periodic circulation are desirable.

Discussion. In the preceding paper it was pointed out that the periodic changes in ventilation produced by moderate obstruction of cerebral blood vessels might be a resultant of two circulatory changes which are occurring periodically and at the same time—namely, changing cerebral flow of blood and changing mean blood pressure. The same possibility holds for the periodic ventilation produced by greater obstruction of the cerebral blood vessels. Data bearing on the relative importance of these two factors are therefore briefly considered.

Considering the central chemical effects of altered flow of blood first, it is believed that normally the respiratory center is provided with an abundant supply of well oxygenated blood and under these conditions is protected against gross and rapid chemical changes, but that with impaired circulation conditions are provided which are susceptible to gross fluctuations which in turn lead to periodicity of circulatory and respiratory functions. Thus when blood flow is sufficiently diminished oxidations are impaired and anaerobic conditions develop. Under these conditions lactic acid accumulates in the brain at a rapid rate (McGinty and Gesell, 1925). There is thus a sudden increase in fixed acids, a sudden liberation of carbonic acid from the tissue bases, and a reduction in the tissue buffer base. These changes are accompanied by a decrease in transport of acid from the tissues. Not only is there a decrease in the physical transport of acid but with the failure of the tissues to get oxygen from the blood there is a broken coördination of the dual function of hemoglobin with a consequent impairment of chemical transport of acids from the tissues. The increase in acidity of the tissues impairs oxidations still more. There is thus a sudden impairment of oxidation and an increase in acidity. The cardio-inhibitory center is markedly stimulated during decreasing volume flow of blood and so is the respiratory center. Both of these conditions lead to a marked increase in ventilation of the blood which raises the oxygenation and lowers the carbon dioxide tension of the blood. Suddenly this highly ventilated blood flows through the respiratory center at an augmented rate and the chemical processes are as quickly reversed. Increased supply of oxygen and high concentration of oxidizable materials lead to supernormal oxidations. Lactic acid is removed by oxidation and by shift to the precursor state (Hill, 1913; Meyerhof, 1921). Base is liberated to combine with free carbon dioxide. The transport of acid is improved by increase in flow of blood, by the lowered carbon dioxide tension of the blood and by

the reëstablishment of the coördination of the dual function of hemoglobin. Apnea comes on and lasts until chemical stimulation is reëstablished.

The changes in periodicity of ventilation may also have been modified by the chemical changes occurring in various parts of the reflex arc for the volume flow of the body as a whole appears to be periodic. The work of Glazer (1927), Winkler (1929), and Gay (1929), who showed the effects of hemorrhage, cyanide and low oxygen mixtures on the response of the striated muscle to reflex, motor nerve and direct stimulation suggest chemical influences outside the respiratory center proper.

To what extent the periodic changes in ventilation and circulation are influenced by vascular reflexes set up by changes in mean blood pressure is difficult to state with certainty. With regard to the heart reflex the findings are more positive. A fall in pressure which should reflexly establish an increase in heart rate is accompanied in our experiments by a marked slowing of the pulse. Thus if the vascular reflex is operating it is relatively weak as compared with the central chemical stimulation of the inhibitory center. But the fact that the central chemical and vascular reflex effects are theoretically additive in the case of respiration offers difficulty in evaluating the quantitative effects of each. Reasoning by inference from the results on heart rate it might be concluded that here too the central chemical effect is the important effect. The difficulty of obtaining periodic respiration, for the present at least, precludes the use of controls in which the vagus nerves are cut.

If the changes in blood flow are the initiating cause of periodic changes in ventilation, as they appear to be in the present experiments, we must attempt to explain periodicity in blood flow. It is only necessary to accept the view (Gesell, 1929) that the metabolism of the circulatory centers is a controlling factor in the regulation of circulation and by a chemical mechanism similar to that controlling ventilation. It is thus assumed that the chemical changes just described for the respiratory center occur within the circulatory centers as well. Experiments 2A, 2B, and 3 show a fall in mean blood pressure associated with a decrease in heart rate, and an increase in blood pressure associated with an increase in heart rate. Thus the cardio-inhibitory and respiratory centers show similar and simultaneous changes in activity.

Experiments in which amytal was used as the anesthetic, marked periodicity occurred without significant changes in heart rate. These experiments thus indicate that periodicity of the vasomotor center may bring about periodicity in mean blood pressure. Since respiratory and circulatory stimulation appear simultaneously with decreasing blood flow, a common stimulating mechanism through increased acidity and impaired oxidations is supported. As for depression of respiratory movements which may follow abruptly on stimulation during decreased flow, it is

pointed out that there can hardly be a more effective mechanism for bringing about complete depression of a nerve center than an impaired supply of oxygen and impaired removal of acid both of which lead to increased acidity which in turn impairs oxidations still more. Thus it is not surprising that when the respiratory center is stimulated to its maximum while the energy of the center is being rapidly depleted, that stimulation should promptly give way to depression. Obviously the resistance of centers must vary and for that reason stimulation of the respiratory center of one animal may carry through the entire period of decreased blood flow and into the next period of increased flow, whereas another may give way during the period of decreased flow. Thus apnea which develops with decreased flow although of different immediate origin is perhaps not so different from the apnea initiated during increasing blood flow. For that reason it may not be profitable to attempt a division of periodic ventilation into distinct types unless it be to divide it into periodic respiration with and without distinct apneas.

SUMMARY

Periodic respiration with pronounced apneas, produced by marked occlusion of cerebral blood vessels, was studied.

The blood flow to the brain was curtailed by three methods; 1, ligation of spinal arteries plus the application of occlusion pressure to one cerebral artery and occlusion of remaining cerebral arteries; 2, increased intracranial pressure, and 3, application of occlusion pressure to one of the four cerebral arteries with the occlusion of the others.

Increasing curtailment of blood flows was accompanied by initial stimulation of respiratory movements, which was followed by a period of partial or complete depression. After this depression, periodicity of ventilation sometimes followed.

The periodicity of ventilation thus established was accompanied by periodic changes in mean blood pressure, volume flow of blood, and heart rate. The respiratory groups were initiated during decreasing flow of blood and decreasing blood pressure. In some experiments they terminated in apnea while blood pressure and blood flow were still decreasing and in others they extended for a short period into the increasing blood pressure and increasing blood flow.

Since apnea was initiated towards the close of decreasing blood flow or beginning of increasing blood flow, it was suggested that apnea was produced by both severe depression and by processes of recovery. Accordingly apneas were designated as depression and recovery apneas.

In experiments in which periodic changes in heart rate occurred, slowing of the heart was in the main associated with decreasing mean blood pressure and decreasing flow of blood, and augmentation with increasing blood

pressure and increasing flow of blood. It is thus suggested that the cardio-inhibitory center is stimulated like the respiratory center by the same chemical mechanism.

It was suggested that the rapid rate and the gross change in chemical state of the medullary centers coupled with impaired functional activity of these centers provide conditions for periodic activity. A decreased blood flow brings about a decrease in the chemical and physical transport of acid, a decrease in oxidations with a consequent broken coördination of the dual function of hemoglobin all resulting in an altered state of oxidations, and increased acidity of the respiratory center and an over ventilation of the blood. An increased blood flow of oxygenated blood now reverses these processes. Oxidative and non-oxidative removal of lactic acid and the liberation of free base and improved transport of acid combine to bring about a new state of oxidation and a decrease in acidity.

The absence of changes in heart rate in one series of experiments with marked periodicity of ventilation, blood pressures, and blood volume flows indicates that periodicity may have its origin in periodic changes of the vasomotor center. However, the volume flow of blood ran parallel in the splanchnic, femoral, submaxillary, and cerebral blood vessels. Direct evidence of active vasomotor changes was, therefore, not obtained.

Our results suggest that periodic chemical stimulation of the circulatory centers produces periodic changes in ventilation of a central chemical origin. Since decreasing blood pressure may reflexly stimulate pulmonary ventilation this phenomenon may be looked upon as a possible modifying factor.

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